Solvent Effects on the Acid Catalysed Hydrolysis of Benzamide, *N*-Methylbenzamide, and *NN*-Dimethylbenzamide

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The rate of hydrolysis of benzamide has been measured over a wide range of acidities in HCl, H_2SO_4, $HClO_4$, and H_3PO_4, that of *N*-methylbenzamide in HCl and H_2SO_4, and that of *NN*-dimethylbenzamide in HCl, H_2SO_4, and $HClO_4$. The basicity constants of these three amides have been measured in HCl and $HClO_4$ and that of benzamide in H_2SO_4 also, and have been found to be non-thermodynamic functions. Interpretation of the rate data by use of existing rate-correlation equations has been found unsatisfactory, but the data do fit a two-term rate equation. Deuterium isotope effects and some Arrhenius parameters have been measured. Oxygen-18 exchange is absent. Measurements of the molar activity coefficient of unprotonated *NN*-dimethylbenzamide have shown that whereas acids salt-in the amide, salts generally salt it out.

THE acid catalysed hydrolysis of amides has been reviewed.[1] The rate-determining step is widely held to involve nucleophilic attack of water on the carbonyl carbon atom of the amide which has been protonated in a pre-equilibrium step. It has been established for some time that amides protonate predominantly on oxygen in strongly acidic media,[1,2] but Liler [3] has recently suggested from a study of the n.m.r. spectra of ^{15}N amides, that in dilute acid protonation is predominantly on nitrogen. Olah [4] has found that at least under conditions where the site of protonation can be followed by n.m.r., there is strong indication that the basic site is on oxygen under kinetic conditions, and *N*-protonation becomes important only under thermodynamically controlled conditions.

We now report rate data measured over an extensive range of acidities for the hydrolysis of benzamide in hydrochloric, sulphuric, and phosphoric acids at 100·4 °C and in perchloric acid in the temperature range 73·8—110·5 °C; for the hydrolysis of *N*-methylbenzamide in hydrochloric and sulphuric acid at 100·4 °C; and for the hydrolysis of *NN*-dimethylbenzamide in hydrochloric, sulphuric, and perchloric acids at 100·4 °C.

Smith and Yates [5] have studied the kinetics of hydrolysis of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide in 5—60% aqueous sulphuric acids over the temperature range 25—85 °C, and found that the order of reactivity with *N*-methyl substitution, namely primary > tertiary > secondary, was the same as we had preliminarily recorded [6] for hydrolysis of these three amides in hydrochloric acid. They attributed the order solely to variations in $\Delta H^\ddagger$ with structure.

One of the major problems in interpreting the rate effects of moderately concentrated acids is that of separating the effects of acids as proton donors from those as electrolytes. One approach is to use mixtures of acids and salts of constant ionic strength, for example lithium and hydrogen chloride which have very similar effects upon water activity.[7] However, this approach can fail if the acid and its salt have very different effects upon the activity coefficient of the substitutent. Therefore in the work described here we also examined the effects of acids and salts upon the activity coefficient of *NN*-dimethylbenzamide. (The properties of this amide are such that these measurements can easily be made on it.)

The deuterium isotope effect has been measured in HCl, and absence of ^{18}O exchange in acid solution has been confirmed.

RESULTS AND DISCUSSION

Basicity Constants.—The original values [8] of pK_{AH^+} at 25 °C (benzamide, −2·16; *N*-methylbenzamide, −2·13; and *NN*-dimethylbenzamide, −1·62) were based on the H_0 acidity scale. The values redetermined

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[1] C. J. O'Connor, *Quart. Rev.*, 1970, **24**, 553.

[2] R. B. Homer and C. D. Johnson, 'The Chemistry of Amides,' ed. J. Zabicky, Interscience, New York, 1970, p. 187.

[3] M. Liler, *Chem. Comm.*, 1971, 115.

[4] G. A. Olah, personal communication.

[5] C. R. Smith and K. Yates, *J. Amer. Chem. Soc.*, 1971, **93**, 6578.

[6] C. A. Bunton, C. J. O'Connor, and T. A. Turney, *Chem. and Ind.*, 1967, 1835.

[7] R. A. Robinson and R. H. Stokes, 'Electrolyte Solutions,' Butterworths, London, 1959.

[8] J. T. Edward, H. S. Chang, K. Yates, and R. Stewart, *Canad. J. Chem.*, 1960, **38**, 1518.

in sulphuric acid by use of the H_A acidity scale[9] are: benzamide, −1·74; *N*-methylbenzamide, −1·7; and *NN*-dimethylbenzamide, −1·4. We have used the last two values for the calculations in sulphuric acid which follow. Bunnett and Olsen[10a] suggested that the H_A function is too negative by *ca.* 0·3 unit, which would affect pK_{AH^+} values determined by use of H_A, and that a more realistic value of pK_{AH^+} for benzamide, determined from the intercept of their linear free-energy relationship, would be −1·53.

We have determined the ionisation ratio I of the conjugate acid of the amide to amide, $[AH^+]/[A]$, for benzamide in hydrochloric, sulphuric, and perchloric acids, and for *N*-methylbenzamide and *NN*-dimethylbenzamide in hydrochloric and perchloric acids. Results are in Table 1.

TABLE 1

Spectrophotometric determination of the ionisation of benzamide (I), *N*-methylbenzamide (II), and *NN*-dimethylbenzamide (III)

	Values of $[AH^+]/[A]$			
t = 25·0 °C				
C_{HCl}/M	1·0	2·0	3·0	4·0
(I) (247 nm)		0·0971	0·193	0·398
(II) (242 nm)		0·174	0·333	0·605
(III) (236 nm)	0·113	0·355	0·731	1·46
C_{HCl}/M	5·0	6·0	7·0	8·0
(I) (247 nm)	0·772	1·68	3·40	
(II) (242 nm)		2·49		7·36
(III) (236 nm)	2·53	5·68		
t = 25·0 °C				
C_{HClO_4}/M	1·6	2·4	3·2	4·0
(I) (240 nm)	0·0880	0·196	0·413	0·759
(II) (240 nm)		0·181	0·313	0·709
(III) (236 nm)	0·133	0·447	0·943	1·55
C_{HClO_4}/M	4·8	5·6	6·4	7·2
(I) (240 nm)	1·57	3·45	6·42	
(II) (240 nm)	1·35	2·91	6·56	8·71
(III) (236 nm)	2·34	4·51		
$C_{H_2SO_4}$/M	2·0	2·27	3·0	4·0
(I) (247 nm, 25·0 °C)		0·813	0·210	0·533
(I) (247 nm, 47·1 °C)	0·110		0·249	0·507
$C_{H_2SO_4}$/M	5·0	6·0	7·0	8·0
(I) (247 nm, 25·0 °C)	1·09	2·25	4·17	8·89
(I) (247 nm, 47·1 °C)		2·02	4·15	10·2

Only values of $\log_{10} I$ in the range ±1 are acceptable for substitution in a plot of $\log_{10} I$ against H_A because the experimental error in this quantity increases rapidly outside this range.[11] Yates and Stevens[9] divided the pK_{AH^+} values of amides into several groups according to their slopes of $\log_{10} I$ against H_A. When the slopes fall between 0·95 and 1·05, pK_{AH^+} can be considered a valid thermodynamic function. When the slopes are outside this range but still close to unity (0·9—1·1) the pK_{AH^+} values have less significance but can be considered approximate.

Table 2 shows the results of plotting $\log_{10} I$ against H_A. Although the slopes are close to unity the basicity constants of amides are not true thermodynamic functions, but differ slightly for the various strong acids. Results for acetanilide[12] extend this observation. We did not detect a large difference in the $-pK_{AH^+}$ values of benzamide measured at 25 and 47 °C, although several workers have reported large decreases in the value of $-pK_{AH^+}$ of 4-nitroaniline with increasing temperature.[13,14] (Most acidity function based parameters decrease with increasing temperature.[14,15])

TABLE 2

Values of $-pK_{AH^+}$ of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide

Amide	t/°C	Acid	$-pK_{AH^+}$	Slope of $\log_{10} I$ *vs.* $-H_A$	c.c
Benzamide	25·0	HCl	1·79	0·99	0·998
	25·0	$HClO_4$	1·70	1·02	0·998
	25·0	H_2SO_4	1·84	1·03	0·998
	47·1	H_2SO_4	1·81	1·00	0·998
N-Methylbenzamide	25·0	HCl	1·59	0·91	0·998
	25·0	$HClO_4$	1·77	1·03	0·994
NN-Dimethylbenzamide	25·0	HCl	1·21	0·94	0·999
	25·0	$HClO_4$	1·47	0·94	0·993

Rate Constants of Hydrolysis.—Table 3 summarises the results obtained for the rate constants, k_ψ, of hydrolysis of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide in acid solutions.

For benzamide k_ψ (max) decreases in the order HCl > H_2SO_4 > $HClO_4$ > H_3PO_4, and the position of the rate maximum (plotted as a function of H_A for HCl, H_2SO_4, and $HClO_4$ and H_0 for H_3PO_4) shifts to lower acidity in the order H_2SO_4 > HCl > $HClO_4$ = H_3PO_4. Because the measured values of pK_{AH^+} also decrease in the order H_2SO_4 > HCl > $HClO_4$ (Table 2) a value of $-pK_{AH^+}$ = 1·70 (*i.e.*, equal to the value of pK_{AH^+} in $HClO_4$) has been used to calculate the values of α in H_3PO_4.

For *N*-methylbenzamide the rate in hydrochloric is much greater than in sulphuric acid except at very low acidity, and the maximum in the profile is at a slightly higher acidity in sulphuric acid in line with the order of basicity constants. In these respects *N*-methylbenzamide shows similar behaviour to benzamide although introduction of one methyl group on the nitrogen atom decreases the reaction rate, which has been attributed to combined steric retardation and possibly hyperconjugative stabilisation.[16] However, *NN*-dimethyl-

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[9] K. Yates and J. B. Stevens, *Canad. J. Chem.*, 1965, **43**, 529.

[10] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44** (*a*) 1899, (*b*) 1917.

[11] W. M. Schubert and R. H. Quacchia, *J. Amer. Chem. Soc.*, 1962, **84**, 3778.

[12] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1972, in the press.

[13] I. R. Biggs, *J. Chem. Soc.*, 1961, 2572; R. H. Boyd and C. H. Wang, *J. Amer. Chem. Soc.*, 1963, **87**, 430.

[14] A. J. Gel'bshtein, G. G. Shchleglova, and M. I. Temkin, *Zhur. neorg. Khim.*, 1956, **1**, 282; C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, 1969, **91**, 6654.

[15] E. M. Arnett and R. D. Bushick, *J. Amer. Chem. Soc.*, 1964, **86**, 1564.

[16] P. D. Bolton, *Austral. J. Chem.*, 1966, **19**, 1013.

benzamide hydrolyses more rapidly than *N*-methylbenzamide. (This apparent anomaly was also noted by Bolton[16] for the hydrolysis of *N*-methylacetamide and *NN*-dimethylacetamide, and he suggested that the amide–solvent interactions might be the disturbing factor for *NN*-disubstituted amides.) Moreover the rate of hydrolysis before the rate maximum is faster in sulphuric acid than in hydrochloric acid, but slower after the maximum, and the position of the maximum shifts to lower acidities in the reverse order of the basicity constants, *i.e.*, HCl > $HClO_4$ > H_2SO_4. Therefore the position of the maximum does not correlate with the magnitude of $-pK_{AH^+}$.

TABLE 3

Rate constants for hydrolysis of benzamide (I), *N*-methylbenzamide (II), and *NN*-dimethylbenzamide (III) in acid solution

Hydrochloric acid at 100·4 °C $10^5k_\psi/s^{-1}$; At 25·0 °C $10^7k_\psi/s^{-1}$

C_{HCl}/M	(I)	C_{HCl}/M	(II)	C_{HCl}/M	(III)	C_{HCl}/M (25·0 °C)	(I) (25·0 °C)
0·08	3·07	0·08	0·576	0·12	1·24	1·42	3·35
1·00	40·8	0·42	2·59	0·60	6·10	2·74	7·30
1·67	65·9	0·84	5·13	1·19	12·2	4·45	8·52
2·51	95·2	1·67	9·77	2·38	19·2	6·05	6·22
3·35	119	2·51	11·8	3·57	24·0	7·67	3·82
4·05	128	3·35	13·3	4·76	22·6	9·45	2·07
4·12	129	4·17	13·2	5·95	20·0		
5·02	119	5·02	11·9	8·10	14·9		
6·47	95·9	6·02	9·60				
8·37	65·5	7·12	7·68				
		8·37	5·12				

Perchloric acid $10^5k_\psi/s^{-1}$

C_{HClO_4}/M	110·5 °C (I)	100·4 °C (I)	92·2 °C (I)	84·0 °C (I)	73·8 °C (I)	C_{HClO_4}/M	100·4 °C (III)
0·12		3·5	2·3	0·9		1·10	6·6
1·00	90	35	20	7·7	4·1	1·67	8·1
1·58	120	51	33			2·10	10·6
2·10				17	5·5	2·78	11·0
2·28	170	63	36			3·17	10·9
2·72	160	71	36	16·5		4·17	6·3
3·33				19·5	9·0	5·10	4·8
3·30	150	70	38			7·05	2·2
4·16	140	51	31	14·5			
5·14	95	39	19	13	5·0		
6·94	30	15	6·3	3·9			
9·12		1·9	0·9	0·5			
11·36		0·9					

Sulphuric acid at 100·4 °C $10^5k_\psi/s^{-1}$

$C_{H_2SO_4}$/M	(I)	(II)	(III)
0·05	5·0	0·30	0·72
1·10	45	3·5	15·0
1·70	60	4·9	20·0
2·35	74	6·1	21·2
2·90		6·5	20·7
3·00	95		
3·75	103	7·3	18·1
4·50	110	6·3	17·2
5·25	89		
6·20	62	4·7	10·7
7·00	38	3·8	
9·00	11·5	2·1	3·2
11·20	5·0	0·60	
13·70	1·5	0·25	
16·05	1·1		
17·75	0·5		

Phosphoric acid at 100·4 °C $10^5k_\psi/s^{-1}$

$C_{H_3PO_4}$/M	(I)
0·04	1·3
1·13	4·1
2·25	8·4
3·55	13·9
5·10	18
6·85	22
8·75	22
10·88	12·5
14·35	4·0
14·60	2·2

The values of H_0, a_w, and H_A for HCl, $HClO_4$, and H_2SO_4 used in the calculations which follow are in ref. 12. The H_0 and a_w values for H_3PO_4 are from refs. 17 and 18 respectively. Where possible the values of a_w and H_0 have been corrected to the temperature of the rate measurements.

Table 4 gives the slopes (w) and correlation coefficients (c.c.) of plots of $(\log_{10} k_\psi - \log_{10} \alpha)$ against $\log_{10} a_w$ (Bunnett w function)[19] and the slopes (ϕ), intercepts ($-\log_{10} k_2^\circ$, the second-order rate constant at infinite dilution in water), and correlation coefficients (c.c.) of plots of $(\log_{10} k_\psi' - \log \alpha)$ against $(H_0 + \log_{10} C_{H^+})$ (Bunnett–Olsen linear free energy relationship).[10b] The correlation coefficients for the Bunnett w plots are poor, but the approximate values of w obtained generally lie in the range 1·2—3·3 said to be characteristic of water acting as a nucleophile in the rate-determining step. The correlation coefficients for the Bunnett–Olsen linear free-energy relationships are better, but the values of ϕ are >0·58, and therefore fall in the region indicative of water acting as a proton-transfer agent. We have previously found values of ϕ which lie outside Bunnett's original classifications for the hydrolysis of acetanilide[12] and *N*-acetylsulphanilic acid.[20]

Empirically we find that the relation between k_ψ and acid concentration fits equation (1) (where $C_{\bar{A}}$ is the

$$k_\psi C_{\bar{A}} = (k_N C_A C_{H^+} + k_O C_{HA^+}) a_w \qquad (1)$$

stoicheiometric amide concentration, and C_A and C_{HA^+} are the respective concentrations of free and *O*-protonated amide). Equation (1) can be written as (2) or (3)

$$k_\psi/\alpha a_w = k_N C_{H^+}(1 - \alpha)/\alpha + k_O \qquad (2)$$

$$k_\psi/[C_{H^+}(1 - \alpha)a_w] = k_N + k_O\alpha/(1 - \alpha)C_{H^+} \qquad (3)$$

where α is the relative amount of HA^+, and k_O and k_N are the rate constants related to the transition states involving oxygen and nitrogen protonation.[6]

Table 5 lists the values of k_O and k_N obtained by use of both equations (2) and (3). The slope of equation (3) gives a good value of k_O but condenses the data for high water activity and therefore the value of k_N becomes uncertain, whereas the slope of equation (2) gives a more reliable value of k_N. The correlation coefficients of these plots are generally very good.

We have reported that rate measurements for hydrolysis of acetanilide[12] in HCl and H_2SO_4 fit equation (1) extremely well, and do not fit Bunnett w[19] or Bunnett–Olsen[10b] criteria of mechanism. It appears that the reverse of this phenomenon may be true, since data for

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[17] E. M. Arnett and G. W. Mach, *J. Amer. Chem. Soc.*, 1966, **88**, 1177.

[18] K. L. Elmore, C. M. Mason, and J. H. Christensen, *J. Amer. Chem. Soc.*, 1946, **68**, 2538.

[19] J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956, 4968, 4973, 4978.

[20] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1972, in the press.

hydrolysis of acetanilide in $HClO_4$ [12] and *N*-acetylsulphanilic acid in H_2SO_4 [20] which give good correlations with the last two criteria do not fit equation (1). Recent calculations [21] on all available literature data on acid-catalysed amide hydrolysis confirm this pattern. Generally the correlation coefficients for the Bunnett–Olsen linear free-energy relationships are better in H_2SO_4 than in HCl or $HClO_4$.

Moodie *et al.*[22] have criticised the two-term rate equation (1) because they consider it unrealistic to cancel γ_{H^+} with $\gamma^{\ddagger}$. Smith and Yates [5] also consider that the idea of a dual mechanism is inconsistent with their observed lack of medium-dependence of $\Delta H_p^{\ddagger}(E_a)$. They state that this mechanism fails to give reasonable or consistent results when tested on all available data and we have confirmed [12, 20, 21] that there are anomalies.

TABLE 4

Analysis of rate data for hydrolysis of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide by use of Bunnett *w* and Bunnett–Olsen linear free-energy relationships

			Bunnett *w*		Bunnett–Olsen l.f.e.r.		
Amide	t/°C	Acid	w	c.c	ϕ	$-\log_{10} k_2^{\circ}$	c.c
Benzamide	100·4	HCl	3·36	0·968	0·73	1·72	0·975
	25·0	HCl	3·19	0·983	0·74	4·96	0·991
	100·4	H_2SO_4	2·59	0·952	0·75	1·76	0·993
	100·4	H_3PO_4	2·90	0·969	0·73	1·70	0·999
	110·5	$HClO_4$	3·82	0·962	0·77	1·52	0·986
	100·4	$HClO_4$	2·58	0·957	0·63	2·03	0·986
	92·2	$HClO_4$	2·82	0·962	0·69	2·23	0·989
	84·0	$HClO_4$	2·64	0·973	0·65	2·60	0·994
	73·8	$HClO_4$	4·99	0·969	0·80	2·80	0·972
N-Methylbenzamide	100·4	HCl	3·87	0·953	0·79	2·76	0·985
	100·4	H_2SO_4	2·13	0·947	0·61	3·08	0·987
NN-Dimethylbenzamide	100·4	HCl	1·98	0·910	0·43	3·05	0·900
	100·4	H_2SO_4	2·87	0·932	0·70	2·72	0·979
	100·4	$HClO_4$	3·38	0·932	0·70	2·93	0·977

TABLE 5

Analysis of rate data for hydrolysis of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide by use of a two-term rate equation

			Equation (2)		Equation (3)	
Amide	t/°C	Acid	$10^5 k_N$/l mol^{-1} s^{-1}	c.c	$10^5 k_O$/s^{-1}	c.c
Benzamide	100·4	HCl	39·2	0·998	149	0·998
	25·0	HCl	0·026	0·984	0·0552	0·995
	100·4	H_2SO_4	42·0	0·997	39·2	0·987
	100·4	H_3PO_4	59·0	0·980	24·1	0·996
	110·5	$HClO_4$	95·6	0·997	38·8	0·992
	100·4	$HClO_4$	37·3	0·999	17·7	0·998
	92·2	$HClO_4$	22·2	0·996	8·69	0·989
	84·0	$HClO_4$	8·36	0·992	6·10	0·999
	73·8	$HClO_4$	4·16	0·977	3·27	0·999
N-Methylbenzamide	100·4	HCl	6·13	0·997	10·9	0·999
	100·4	H_2SO_4	3·23	0·998	5·41	0·994
NN-Dimethylbenzamide	100·4	HCl	7·15	0·993	37·0	0·999
	100·4	H_2SO_4	14·9	0·994	10·0	0·994
	100·4	$HClO_4$	6·32	0·997	4·59	0·999

One reason for this may be that the parameters a_w and H_0 in the various equations can be temperature-corrected for H_2SO_4, but values are not known over a range of temperatures for the other acids. Bunnett and Olsen,[10a] however, state that kinetic data in perchloric acid do not always afford lineal linear free-energy relation ship plots, whereas data in sulphuric acid appear to give a usual pattern of uniformly linear correlations. They suggest that more data to substantiate or refute these indications would be desirable, and the data in Table 4 seem to substantiate it.

We have tested [21] all of their data for hydrolysis of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide in 5—60% aqueous sulphuric acids over the temperature range 25—85 °C using the above three criteria. As with our own data, correlation coefficients for Bunnett *w* plots were poor, but the correlation coefficients for the Bunnett–Olsen linear free-energy relationships were good (0·993—0·999). Application of equation (1) to their data gave correlation coefficients 0·994—0·999.

As an empirical observation the two-term rate equation

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[21] J. W. Barnett, C. J. Hyland, and C. J. O'Connor, *J.C.S. Chem. Comm.*, 1972, 720.

[22] V. C. Armstrong D. W. Farlow and R. B. Moodie, *J. Chem. Soc.* (*B*), 1968, 1099.

(1) does fit many data very well, but its formulation can be no more than speculative since the conclusions that k_O and k_N are rate constants related to transition states involving oxygen and nitrogen protonation require many assumptions (in particular with respect to activity-coefficient behaviour).

TABLE 6

Arrhenius parameters for hydrolysis of benzamide in perchloric acid

C_{HClO_4}/M	1·06	2·00	3·00	4·18	5·12	6·00	6·96	9·36
$\log_{10} A$	10·1	9·16	9·31	9·41	9·38	9·48	9·58	8·63
E_a/kcal mol^{-1}	23·2	21·2	21·3	21·7	21·9	22·4	22·9	22·8

Temperature Effects.—The values of the Arrhenius parameters for hydrolysis of benzamide in perchloric acid are in Table 6. As in sulphuric acid,[5] the values of E_a are essentially medium-independent, and are consistent with a bimolecular mechanism of hydrolysis.

TABLE 7

Comparison of rate constants of hydrolysis of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide in HCl and DCl

Benzamide

t/°C	C_{HCl}/M	C_{DCl}/M	10^5k_ψ/s^{-1}	$k/_{H_2O}k_{D_2O}$ ‡
25·0	1·01		0·0202	0·75
		1·06	0·0268	
	6·70		0·522	1·09
		6·81	0·483	
100·4	1·07		42·0	0·87
		1·07	48·3	
	6·35		97·5	1·11
		6·35	87·5	

N-Methylbenzamide

t/°C	C_{HCl}/M	C_{DCl}/M	10^6k_ψ/s^{-1}	k_{H_2O}/k_{D_2O} [a]
25·0	1·01		0·0200	0·75
		1·06	0·0267	
	6·70		0·0676	1·06
		6·81	0·0634	

NN-Dimethylbenzamide

t/°C	C_{HCl}/M	C_{DCl}/M	10^6k_ψ/s^{-1}	k_{H_2O}/k_{D_2O} [a]
25·0	1·01		0·178	0·93
		1·06	0·192	
	6·70		0·151	1·08
		6·81	0·141	
100·4	1·01		102	0·87
		1·01	107	
	6·25		192	1·14
		6·25	169	

[a] The reciprocals of these values are given in error in ref. 6.

Deuterium Isotope Effect.—The solvent deuterium kinetic isotope $k(H_2O)/k(D_2O)$ (Table 7) is as expected less than unity at low acidities where the substrate is largely unprotonated, and becomes greater than unity when the substrate is extensively protonated. These observations are consistent with a *A*-2 mechanism for hydrolysis of a moderately basic substrate.[23,24]

^{18}O *Exchange Reaction.*—Several workers[25,26] have shown, over a wide range of acid concentrations, that there is no oxygen exchange during the acid hydrolysis of benzamide. We have shown that there is also no exchange of oxygen atoms during the acid hydrolysis of *N*-methylbenzamide and *NN*-dimethylbenzamide (Table 8). Exchange studies were carried out on both sides of the rate maximum.

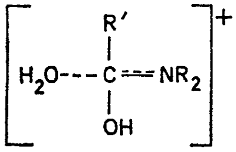
TABLE 8

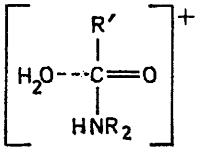
^{18}O Exchange during the acid-catalysed hydrolysis of *N*-methylbenzamide and *NN*-dimethylbenzamide at 100·4 °C

	Atom % excess of abundance				
C_{HCl}/M	H_2O	PhCONHMe		$PhCONMe_2$	
0·84	0	0·897 [a]	0·892 [b]		
9·37	0	0·897 [a]	0·893 [b]		
1·13	0·950			0 [a]	0·013 [b]
5·65	0·950			0 [a]	0·007 [b]

[a] Initial. [b] After one half-life.

Absence of oxygen exchange is consistent with hydrolysis taking place *via* either oxygen (A) or nitrogen (B) protonated transition states. Although it is generally accepted that amides protonate predominantly on oxygen, Smith and Yates[5] suggest that it is possible that amides hydrolyse *only* by way of the much less predominant *N*-protonated form. In either case reaction could occur by an S_N2-like displacement, and a covalent intermediate could go on to products rather than revert to reactants. In addition there could be return to reactants from an intermediate whose life was too short for oxygen equilibration by proton transfer.


(A)


(B)

There is extensive oxygen exchange in the basic hydrolysis of benzamide[25-27] and *N*-methylbenzamide,[27] but not with *NN*-dimethylbenzamide.[27]

Activity Coefficients.—We measured the effect of acids (hydrochloric and perchloric), hydrochloric acid at constant ionic strength μ (6·00 with lithium chloride),

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[23] See refs. in R. P. Bell, ' The Proton in Chemistry,' Methuen, London, 1959.

[24] J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, 1956, **78**, 6008; 1958, **80**, 4162; C. A. Bunton and V. J. Shiner, *ibid.*, **83**, 3207.

[25] M. L. Bender, R. D. Ginger, and K. C. Kemp, *J. Amer. Chem. Soc.*, 1954, **76**, 3350; M. L. Bender and R. D. Ginger, *ibid.*, 1955, **77**, 348; H. Ladenheim and M. L. Bender, *ibid.*, 1960, **82**, 1895.

[26] W. H. Mears and H. Sobotka, *J. Amer. Chem. Soc.*, 1939, **61**, 880; C. A. Bunton, T. A. Lewis, and D. R. Llewellyn, *Chem. and Ind.*, 1954, 1154.

[27] C. A. Bunton, B. Nayak, and C. O'Connor, *J. Org. Chem.*, 1968, **33**, 572.

and that of different salts upon the distribution of *NN*-dimethylbenzamide between water and hexane at 25·0 °C. In order to do this we had to take into account the acid protonation of the amide, and we assumed that the protonated amide would be insoluble in hexane. The results are in Tables 9—12. The values of the activity coefficient f have been calculated from the experimentally measured value of $I_M = [AH^+]/[A]$.

TABLE 9

Effect of perchloric acid upon the molar activity coefficient of *NN*-dimethylbenzamide at 25·0 °C

$\bar{A} = 3{\cdot}366$, $A_{org}^{\circ} = 1{\cdot}362$, $A_w^{\circ} = 2{\cdot}004$, $A_w^{\circ}/A_{org}^{\circ} = 1{\cdot}47$

C_{HClO_4}/M	A_{org}	$\bar{A} - A_{org}$	I_M	A_w	A_w/A_{org}	f
1·00	0·801	2·57	0·113	2·26	2·83	0·52
2·00	0·384	2·98	0·447	2·06	5·37	0·27
3·00	0·140	3·23	0·943	1·66	11·9	0·12
4·00	0·038	3·33	1·55	1·31	34·3	0·043
5·00	0·014	3·35	2·34	1·00	71·6	0·021

TABLE 10

Effect of hydrochloric acid upon the molar activity coefficient of *NN*-dimethylbenzamide at 25·0 °C

C_{HCl}/M	1·00	2·00	3·00	4·00	5·00	6·00
f	0·71	0·71	0·52	0·37	0·31	0·17

TABLE 11

Effect of hydrochloric acid at constant ionic strength (6·00 with lithium chloride) upon the molar activity coefficient of *NN*-dimethylbenzamide at 25·0 °C

$\bar{A} = 5{\cdot}234$, $A_{org}^{\circ} = 2{\cdot}119$, $A_w^{\circ} = 3{\cdot}115$, $A_w^{\circ}/A_{org}^{\circ} = 1{\cdot}47$

C_{HCl}/M	C_{LiCl}/M	A_{org}	$\bar{A} - A_{org}$	I_M	A_w	A_w/A_{org}	f
1·0	5·0	1·70	3·54	1·93	1·21	0·712	2·07
2·0	4·0	0·827	4·41	2·39	1·30	1·57	0·93
3·0	3·0	0·474	4·76	2·55	1·34	2·83	0·52
4·0	2·0	0·310	4·92	2·61	1·37	4·40	0·33
5·0	1·0	0·152	5·08	3·15	1·22	8·05	0·18
6·0		0·103	5·13	4·79	0·886	8·60	0·17

Note: These values of f are relative to water as the standard state. For $C_{LiCl} = 6$M the molar activity coefficient of *NN*-dimethylbenzamide = 3·48 (see Table 12).

TABLE 12

Effect of added salts upon the molar activity coefficient of *NN*-dimethylbenzamide at 25·0 °C

C_{salt}/M	1·00	2·00	4·00	6·00
	Molar activity coefficient f			
NaCl	1·58	2·63	7·17	
KCl	1·58	2·41	6·88	
LiCl		1·64	2·40	3·48
$NaClO_4$	0·928	0·98	1·41	
$NaC_7H_7SO_3$	0·531	0·27		

In the calculations (shown in Table 13) we have used absorbances instead of concentration, assuming of necessity that the extinction coefficient in water and aqueous acid is approximately the same as the extinction coefficient in hexane, *i.e.*, $\varepsilon_w = \varepsilon_{org}$.

The variations of activity coefficient of unprotonated *NN*-dimethylbenzamide with added salts are similar to those found for many polar non-electrolytes[28] in that, lithium, sodium, and potassium chloride ' salt-out ' the amide, sodium tosylate ' salts it in,' as does sodium perchlorate in low concentration. However, perchloric and hydrochloric acids salt-in the amide very strongly. As expected, perchloric acid is particularly effective, and the activity coefficient decreases in mixtures of HCl and LiCl as lithium is replaced by hydronium ion. The hydronium ion is therefore sharply different from the alkali-metal cations in its ability to salt-in the unprotonated amide, probably because it stabilises the amide by increasing the amount of hydrogen bonding to it.

TABLE 13

$\bar{A}$ = total concentration of the amide
A_w = absorbance of ' free ' amide in the aqueous layer ($H_3O + H^+$ or + salt)
A_{org} = absorbance of ' free ' amide in the organic layer
A_w°(AD) = absorbance of ' free ' amide in water after distribution (AD) with hexane
A_{org}°(AD) = absorbance of ' free ' amide in the organic layer after distribution with water
AH_w^+ = absorbance of protonated amide (in the aqueous layer)

$$I = AH_w^+/A_w$$
$$\bar{A} = \{A_{org} + A_w + AH_w^+\}\,(\mathrm{AD})$$
$$= \{A_{org} + A_w + A_wI\}\,(\mathrm{AD})$$
$$= \{A_{org} + A_w(1 + I)\}\,(\mathrm{AD})$$
$$A_w(\mathrm{AD}) = \{\bar{A} - A_{org}(\mathrm{AD})\}/(1 + I)$$
$$A_w^{\circ}(\mathrm{AD}) = \bar{A} - A_{org}^{\circ}(\mathrm{AD})$$
$$f = \{A_w^{\circ}(\mathrm{AD})/A_{org}^{\circ}(\mathrm{AD})\}/\{A_w(\mathrm{AD})/A_{org}(\mathrm{AD})\}$$

TABLE 14

Effect of hydrochloric acid at constant ionic strength μ upon the rate constants of hydrolysis of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide

Benzamide at 25 °C

Hydrochloric acid + lithium chloride (μ = 6·00)

C_{HCl}/M	1·00	2·00	3·00	4·00	5·00	6·00
10^7k_ψ/s^{-1}	3·59	5·32	6·08	6·15	6·70	6·93

Benzamide at 100·0 °C

Hydrochloric acid + lithium chloride (μ = 10·00)

C_{HCl}/M	4·00	6·00	7·60	10·00
10^5k_ψ/s^{-1}	43·4	46·5	43·4	41·5

N-Methylbenzamide at 50·0 °C

Hydrochloric acid + lithium chloride (μ = 6·00)

C_{HCl}/M	1·00	3·00	6·00
10^7k_ψ/s^{-1}	3·35	5·71	6·33

N-Methylbenzamide at 100·0 °C

Hydrochloric acid + lithium chloride (μ = 6·00)

C_{HCl}/M	1·00	3·00	6·00
10^5k_ψ/s^{-1}	3·26	6·56	8·06

NN-Dimethylbenzamide at 25·0 °C

Hydrochloric acid + lithium chloride (μ = 6·00)

C_{HCl}/M	1·00	3·00	6·00
10^7k_ψ/s^{-1}	2·78	2·73	2·28

We have carried out kinetic measurements on the hydrolysis of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide in HCl–LiCl mixtures for the most part so that we could compare the kinetic data with the activity coefficients measured. Results are in Table 14.

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[28] F. A. Long and W. F. McDevit, *Chem. Rev.*, 1952, **51**, 119.

One problem with any treatment of acid hydrolysis which uses water activity as a kinetic parameter is that protonating power of the acid, the activity coefficients of the initial and transition states, and the water activity may not be independent parameters,[29,30] and the success of equation (1) in fitting the rate data does not prove that only one water molecule is involved in formation of the transition state. Mixtures of HCl and LiCl of constant ionic strength have almost constant water activities,[7] and therefore the rates were measured in these mixtures. The rate maximum is then less evident (Table 14).

We had hoped that these results might provide a test of the two-parameter equation (1) because water activity is approximately constant in HCl–LiCl mixtures of constant ionic strength.[7] However, it became clear that the treatment would probably break down, because Li^+ and H^+ have different effects upon the activity coefficient of the amide. These differences should cause a failure of two-term, or any other, rate equation in these mixtures of acid and salt (*cf.* the similar conclusions reached in considering anhydride hydrolysis [29b]).

EXPERIMENTAL

Materials.—AnalaR benzamide was recrystallised from hot water and had m.p. 126·5—127·0 °C. *N*-Methylbenzamide, [^{18}O]-*N*-methylbenzamide, and *NN*-dimethylbenzamide were prepared as in ref. 27. Concentrated AnalaR hydrochloric, perchloric, sulphuric, and phosphoric acids were standardised against sodium hydroxide, and were diluted with deionised water by weighing to give solutions of the required molarity.

Solutions of deuterium chloride were made by saturating deuterium oxide with dry hydrogen chloride and then diluting this solution with deuterium oxide (MCB, 99·8% purity).

Hexane was an MCB product, Spectroquality.

Ionisation Spectra.—The changes in the spectra of benzamide with increasing concentrations of hydrochloric and perchloric acids at 25·0 °C and sulphuric acid at 25·0 and 47·1 °C, and of *N*-methylbenzamide and *NN*-dimethylbenzamide in increasing concentrations of hydrochloric and perchloric acids at 25·0 °C were measured on a Cary 14 spectrophotometer.

Kinetic Measurements.—The hydrolysis of benzamide in hydrochloric acid was followed by determining the evolved ammonia by use of Nessler's reagent. The hydrolysis in sulphuric, perchloric, and phosphoric acids and in solutions of (HCl + LiCl) were followed spectrophotometrically between 210 and 230 nm. The first-order rate constant, k_ψ, was calculated from the slope of the line obtained by plotting $\log_{10}(\mathrm{OD}_\infty - \mathrm{OD}_t)$ against t, where OD_t was the optical density of the solution at time t. The optical density at infinite time OD_∞ was determined on a sample which had reacted for *ca.* 8—10 half-lives.

The hydrolyses of *N*-methylbenzamide and *NN*-dimethylbenzamide were followed spectrophotometrically using spectra recorded from 207 to 232 nm.

Values of k_ψ were calculated for at least two wavelengths and the average values of such calculations are quoted in Tables 3, 7, and 14. The accuracy of the results are generally ±2%, and is reflected in the number of significant figures quoted in these Tables.

Activity Coefficients.—A known volume of the stock solution of *NN*-dimethylbenzamide ($3·5 \times 10^{-3}$M) in hexane (between 1 and 10 ml, made up to 10 ml with pure hexane when necessary) was shaken for 1 min at 25·0 °C in a jacketed separating funnel with the aqueous solution (2 ml) of the acid or salt. The amide in the organic layer was measured at 218 nm in a Gilford spectrophotometer, with hexane as blank. The concentration of the remaining amide (protonated and/or ' free ') was calculated as indicated. The molar activity coefficients, f, were calculated relative to water as the standard state.

^{18}O Exchange during Acid-catalysed Hydrolysis.—The extent of ^{18}O exchange between [^{18}O]*N*-methylbenzamide and H_2O and *NN*-dimethylbenzamide and $H_2{}^{18}O$ during the hydrolyses was determined at 100·4 °C.

The experimental conditions and methods of determining the isotope abundances were similar to those already described.[27]

Least-squares analyses and calculations of k_N and k_O for the two-term rate equation were carried out on an I.B.M. 1130 computer.

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[29] C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, (*a*) 1965, **30**, 1365; (*b*) 1966, **31**, 3764.

[30] C. A. Bunton, J. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, 1968, **90**, 1258.